Short Communication

Serum Antibodies to *Helicobacter pylori* and the CagA Antigen Do Not Explain Differences in the Prevalence of Precancerous Gastric Lesions in Two Chinese Populations with Contrasting Gastric Cancer Rates[1]

Frank D. Groves,[2] Guillermo Perez-Perez, Lian Zhang, Wei-cheng You, Stuart R. Lipsitz, Mitchell H. Gail, Joseph F. Fraumeni, Jr., and Martin J. Blaser

Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland 20892-7244 [F. D. G., W-c. Y., M. H. G., J. F. F.]; Department of Internal Medicine, New York University School of Medicine, New York, New York 10016 [G. P-P., M. J. B.]; Beijing Institute for Cancer Research and School of Oncology, Peking University, Beijing, People's Republic of China 100034 [L. Z., W-c. Y.]; Department of Biometry and Epidemiology, Medical University of South Carolina, Charleston, South Carolina 29425-0835 [F. D. G., S. R. L.]; and Veterans' Affairs Medical Center, New York, New York 10010 [M. J. B.]

Abstract

Incidence and mortality rates for gastric cancer in rural People's Republic of China differ greatly over short distances. In Shandong Province, we studied asymptomatic adult subjects from Bei Duan village (*n* = 196) in Linqu County (a high-risk area for gastric cancer) and from Shi Huang village (*n* = 192) in Cangshan County (a low-risk area for gastric cancer). The prevalence of advanced precancerous gastric lesions (APGL) was assessed by microscopic examination of endoscopic stomach biopsies. ELISAs were used to detect serum IgG to *Helicobacter pylori* whole-cell antigen and to the CagA protein. A logistic regression model was used to quantify the role of the two *H. pylori* seromarkers in explaining the differences in prevalence of APGL between the two villages after adjusting for age and sex.

The prevalence of APGL was much greater in Bei Duan than in Shi Huang. Although *H. pylori* seroprevalence by the whole-cell ELISA was similar in the two populations, seroprevalence of CagA was significantly greater in Bei Duan. Although age, sex, and both *H. pylori* seromarkers were associated with APGL in the logistic regression model, the effect of village of residence remained strong after adjustment for all four covariates. Only a relatively small proportion of the difference in prevalence of APGL between these two rural Chinese populations can be explained by differences in *H. pylori* or CagA seroprevalence.

Introduction

Extremely high gastric cancer mortality rates of 70 (per 100,000, age-adjusted to the world standard population) in men and 26 in women (1) are found in Linqu County of Shandong Province, compared with only 5 for males and 3 for females in Cangshan County, located only 200 miles away (2). *Helicobacter pylori* seroprevalence among adult males in 46 rural Chinese counties is highly correlated with gastric-cancer mortality (3), and *H. pylori* colonization has been linked to preneoplastic gastric lesions in Linqu (4).

Although *H. pylori* strains are heterogeneous (5), the majority possess *cagA* (6–9), which encodes CagA,[3] an immunodominant protein antigen (10). In prospective cohort studies of *H. pylori*-positive subjects in The Netherlands and Hawaii, those who were CagA seropositive were twice as likely to develop atrophic gastritis (11), nine times as likely to develop intestinal metaplasia (11), and twice as likely to develop adenocarcinoma of the distal stomach (12), compared with those who were CagA seronegative. A similar cohort study in California indicated that the risk of developing gastric adenocarcinoma was ~3-fold higher among subjects carrying *cagA+* *versus cagA-* strains (13).

In an endoscopic survey in Shi Huang, a village in Cangshan, only 13.5% of subjects had intestinal metaplasia or dysplasia, compared with 45.1% in 14 villages in Linqu (14). In Shi Huang, 55% of subjects were seropositive for *H. pylori*, compared with 72% in Linqu (4). In view of the higher risks of gastric cancer associated with CagA+ strains of *H. pylori* (11–13), we undertook a study to determine whether whole-cell seropositivity to *H. pylori* and/or CagA seropositivity could account for the higher prevalence of APGL in Linqu County than in Shi Huang. In particular, we compared findings in Shi Huang with those in Bei Duan, a village in Linqu County.

Subjects and Methods

Study Populations. Residents 35–64 years of age in Bei Duan village (population 1281) of Linqu County and in Shi Huang village (population 3271) of Cangshan County were invited to participate in the study. The mean ages of study participants were 50.7 (SE = 0.6) years in Bei Duan (52% male) and 48.9 (SE = 0.7) years in Shi Huang (51% male).

Gastric Histopathology. Health officials visited each person 35–64 years of age in village rosters and offered a consent form to invite participation in gastric-cancer screening. All residents were invited except those who were ill or disabled. Participants were given a brief physical examination, their medical histories were recorded, and sera were collected by venipunc-

Table 1   Cross tabulation of APGL, sex, village, and *H. pylori* and CagA Serostatus

H. pylori serologic status[a]		APGL status[b]	Number and percentage of males with APGL					Number and percentage of females with APGL				
			Bei Duan (n = 99)		Shi Huang (n = 100)		P[c]	Bei Duan (n = 93)		Shi Huang (n = 96)		P[c]
Whole-Cell	CagA		n	% (95% CI[d])	n	% (95% CI[d])		n	% (95% CI)	n	% (95% CI)	
+	+ (136)	+ (59)	28	78 (64–91)	4	16 (2–30)	<0.0001	19	48 (32–63)	8	23 (9–37)	0.05
		− (77)	8	22 (9–36)	21	84 (70–98)		21	52 (37–68)	27	77 (63–91)	
	− (82)	+ (22)	9	50 (27–73)	4	15 (1–28)	0.03	6	32 (11–52)	3	17 (0–34)	0.50
		− (60)	9	50 (27–73)	23	85 (72–99)		13	68 (48–89)	15	83 (66–100)	
	All (218)	+ (81)	37	69 (56–81)	8	15 (6–25)	<0.0001	25	42 (30–55)	11	21 (10–32)	0.02
		− (137)	17	31 (19–44)	44	85 (75–94)		34	58 (45–70)	42	79 (68–90)	
−	+ (33)	+ (13)	6	46 (19–73)	1	20 (0–55)	0.63	5	45 (16–75)	1	25 (0–67)	0.91
		− (20)	7	54 (27–81)	4	80 (45–100)		6	55 (25–84)	3	75 (33–100)	
	− (137)	+ (19)	11	34 (18–51)	2	5 (0–11)	0.002	5	22 (5–39)	1	3 (0–8)	0.04
		− (118)	21	66 (49–82)	41	95 (89–100)		18	78 (61–95)	38	97 (92–100)	
	All (170)	+ (32)	17	38 (24–52)	3	6 (0–13)	0.0006	10	29 (14–45)	2	5 (0–11)	0.008
		− (138)	28	62 (48–76)	45	94 (87–100)		24	71 (55–86)	41	95 (89–100)	
All (388)	All (388)	+ (113)	54	55 (45–64)	11	11 (5–17)	<0.0001	35	38 (28–47)	13	14 (7–20)	0.0003
		− (275)	45	45 (36–55)	89	89 (83–95)		58	62 (53–72)	83	86 (80–93)	

[a] Seropositivity status and number of subjects in each stratum (in parentheses).
[b] APGL status is indicated by + or −, and number of subjects in each stratum (in parentheses).
[c] Continuity-adjusted χ^2 test.
[d] CI, confidence interval.

ture. Subjects who had significant blood-clotting disorders, high blood pressure, liver disease, or chronic obstructive pulmonary disease were excluded from further examination. Subjects in both villages underwent endoscopy in 1994, with biopsies taken from up to seven standard sites in the stomach (in Bei Duan) or from a subset of up to four standard sites (in Shi Huang). Because subjects in Shi Huang had at most four biopsies, only these four standard sites were used in comparing the histological scores of subjects from the two villages. There were 747 eligible adults in Shi Huang village, 224 (30%) of whom consented to participate and underwent endoscopy. Insufficient biopsy material was obtained from 10 of these subjects, and 196 (92%) of the remaining 214 also had serology and interview data and were included in the present analysis (2). Of the 292 adults 35–64 years of age in Bei Duan village, 277 were invited to participate in the study, and 263 of these were interviewed and examined; two subjects failed this physical examination. Endoscopic examinations were completed on 239 of the remaining 261 subjects (86% of those recruited); 218 had sufficient tissue samples, and 192 also had serology and interview data and were included in the present analysis.

Biopsies were preserved in 10% neutral buffered formalin, embedded in paraffin, and sectioned at the BICR (Beijing, People's Republic of China). Each slide was reviewed independently according to the protocol of the Chinese Association of Gastric Cancer (15) by three senior pathologists at BICR; these pathologists were not aware of the serostatus or village of residence of the subject. Any discrepancies were resolved by consensus. The lesions of interest, in increasing order of severity, were as follows according to established diagnostic criteria (16): (*a*) superficial gastritis; (*b*) chronic atrophic gastritis; (*c*) intestinal metaplasia; and (*d*) dysplasia. Each biopsy was given a global diagnosis based on the most advanced lesion, and then each subject was assigned a global diagnosis based on the most advanced lesion among any of the four biopsies. We use the term "APGL" to denote intestinal metaplasia or dysplasia. In a separate quality-control study, two senior pathologists from China and the United States with expertise in gastric cancer [Drs. Ji-You Li (BICR) and Pelayo Correa (Louisiana State University, Baton Rouge, LA)] examined 270 slides selected

from subjects in the larger cohort from which the study population in Bei Duan was drawn. This sample consisted of 200 randomly selected subjects, 30 cases with presumptive diagnoses of gastric carcinoma and 40 cases with presumptive diagnoses of dysplasia. Drs. Li and Correa achieved consensus on 267 (98.9%) of the slides; diagnoses for the remaining three slides were either mild or borderline dysplasia (17).

Helicobacter pylori **Serology.** Serological testing was performed by personnel who were not aware of the histological diagnoses. Serum samples were tested for the presence of IgG to the *H. pylori* whole-cell antigens by a previously described ELISA (18, 19). The pooled antigen was derived from an equal mixture of sonicates from five strains from the United States (84-180, 84-182, 84-183, 86-63, 86-86) and used at a concentration of 1 μg/well. Previous studies showed little difference in sensitivity and specificity between whether a United States or Chinese antigen pool was used (19, 20). All serum samples were diluted 1:800 and examined in duplicate wells on 2 different days. Appropriate blanks and positive and negative controls were included in each assay as described (18). We define "*H. pylori* seropositive" as a positive whole-cell antigen ELISA.

CagA status was determined by ELISA to detect serum IgG antibodies to ORV220, a 65-kDa recombinant CagA truncated protein purified from *Escherichia coli*, and positivity was defined as $A \geq 0.30$/nm as validated previously (21). Samples were diluted 1:100 and examined in duplicate wells on two different days.

Statistical Analysis. Differences between the two villages for the prevalence of APGL, as well as for the *H. pylori* whole-cell and CagA serostatus, were tested using the continuity-adjusted two-tailed χ^2 test with one degree of freedom (22). The effect of village of residence on the prevalence of APGL was modeled by unconditional logistic regression (23), adjusting for sex, age group (<50 *versus* ≥50 years), and *H. pylori* whole-cell and CagA serostatus. Ninety-five percent confidence intervals are shown in parentheses (Table 1). Unreported data from Linqu County indicates that the intraclass correlation for APGL is

Table 2   Estimates of odds ratios from logistic regression model of risk factors for advanced precancerous gastric lesions[a]

Variable	Univariate models	Full model	Reduced models			
			Stratified by sex		Stratified by village	
	Crude odds ratios	Adjusted odds ratios	Male (*n* = 199)	Female (*n* = 189)	Bei Duan (*n* = 192)	Shi Huang (*n* = 196)
Sex (male versus *female*[b])	1.4 (0.9–2.2)	0.9 (0.4–2.1)			2.3 (1.2–4.2)	0.8 (0.3–2.1)
Village (Bei Duan versus *Shi Huang*)	6.2 (3.7–10.3)	3.8 (1.8–8.1)	10.1 (4.6–22.2)	3.9 (1.8–8.3)		
Age group (≥50 versus <50 years)	1.9 (1.2–2.0)	2.1 (1.3–3.4)	1.7 (0.9–3.5)	2.4 (1.2–5.0)	1.8 (1.0–3.4)	2.7 (1.1–6.9)
H. pylori (A≥1.00/nm versus A<1.00/nm)	2.6 (1.6–4.1)	2.0 (1.1–3.5)	2.4 (1.1–5.3)	1.6 (0.7–3.9)	1.9 (1.0–3.6)	2.9 (0.9–9.3)
CagA (A≥0.30/nm versus A<0.30/nm)	3.2 (2.0–5.1)	2.3 (1.4–4.0)	2.2 (1.0–4.7)	2.4 (1.1–5.5)	2.5 (1.3–4.8)	1.8 (0.6–5.0)
Sex-village interaction term		2.6 (0.9–7.6)[c]				

[a] Intestinal metaplasia and dysplasia.
[b] Referent group italicized.
[c] *P* = 0.08 for sex-village interaction.

only 0.019.[4] Thus there was no need to adjust the analyses for the presence of more than one subject in some households.

Results

The seroprevalence of *H. pylori* colonization, as determined by the whole-cell ELISA, did not differ significantly between the two villages (54/99 = 55% in Bei Duan *versus* 52/100 = 52% in Shi Huang for males; 59/93 = 63% *versus* 53/96 = 55% for females). However, CagA seropositivity was higher in Bei Duan than in Shi Huang (49/99 = 49% *versus* 30/100 = 30% for males, *P* = 0.008; 51/93 = 55% *versus* 39/96 = 41% for females, *P* = 0.05). Altogether, 71% and 58% (*P* = 0.009) of the subjects in Bei Duan and Shi Huang villages, respectively, were seropositive by either the whole-cell or the CagA assay (data not shown). Many subjects who were seronegative by the whole-cell ELISA were seropositive for CagA, and it was among this subset that the differences in CagA seroprevalence between Bei Duan and Shi Huang, both among males (13/45 = 29% *versus* 5/48 = 10%, *P* = 0.05) and among females (11/34 = 32% *versus* 4/43 = 9%, *P* = 0.02), were most pronounced (data not shown). Among the subjects who were *H. pylori* seropositive by the whole-cell ELISA, the differences in CagA serology were small (67% *versus* 48% in males, *P* = 0.08; 68% *versus* 66% in females).

Table 1 is a cross-tabulation of the prevalence of APGL with *H. pylori* and CagA serostatus in the two villages. The prevalence of APGL was much higher in Bei Duan than in Shi Huang, particularly among males (55% *versus* 11%, *P* < 0.0001), but also among females (38% *versus* 14%, *P* = 0.0003). Within each village and *H. pylori* serostatus, the frequency of APGL was higher in CagA-positive subjects. Subjects in Bei Duan had a higher proportion of APGL, regardless of their *H. pylori* or CagA status. The proportion of subjects with APGL in each village was similar among those who were *H. pylori* positive but CagA negative and those who were *H. pylori* negative but CagA positive.

Separate univariate logistic regressions of the presence of APGL on each of five potential explanatory variables in turn yielded the following unadjusted odds ratios (Table 2): 6.2 for village of residence, 3.2 for CagA, 2.6 for *H. pylori*, 1.9 for age group, and 1.4 for sex. These coefficients were similar to those obtained from a multivariate model that included all five vari-

ables but no interactions (data not shown). Because the interaction term for male sex and residence in Bei Duan village approached statistical significance (*P* = 0.08), this interaction was included in the final model, and stratified analyses were performed to compare two sets of reduced models (Table 2). When the models were stratified by village of residence, the odds ratio for male sex was 2.3 in Bei Duan but only 0.8 in Shi Huang. When the models were stratified by sex, the odds ratio for residence in Bei Duan was 10.1 for males, but only 3.9 for females. However, regardless of which model was chosen, the effect of residing in Bei Duan rather than Shi Huang was stronger than the effects of the other factors (Table 2).

Discussion

As anticipated from previous comparisons of Shi Huang village in Cangshan with 14 villages in Linqu (14), the prevalence of APGL was greater in the village of Bei Duan in Linqu than in Shi Huang, and the same was true of CagA seroprevalence. The finding of similar whole-cell *H. pylori* seroprevalence in the two villages was unexpected in view of the higher seroprevalences found in other villages in Linqu County (4), although the trend was in the expected direction. Perhaps Shi Huang is somewhat atypical in this respect because the 95% confidence interval on the seroprevalence was 46–61%. Also, because of the rather low response rate in Shi Huang (196/747, 26%, included in the final study), the Shi Huang subjects may not be representative of the eligible population in that village. If agreement to participate were associated with being infected with *H. pylori* (*e.g.*, those with symptoms more likely to agree), then the population seroprevalence would be biased upward.

Whole-cell seropositivity and CagA seropositivity were independent risk factors in models also containing age and sex, both in Bei Duan and in Shi Huang. Thus, both indicators of *H. pylori* presence were associated with increased risk of gastric cancer, which is consistent with data elsewhere (11–13). Nonetheless, the effect of village on risk was virtually the same in univariate analyses as in analyses that were adjusted for age, sex, whole-cell seropositivity, and CagA seropositivity. Thus, these factors do not account for the >6-fold greater odds of APGL in Bei Duan than in Shi Huang. Other factors, such as the high consumption of garlic in Shi Huang (2) or the lower *H. pylori* prevalence among children in Shi Huang (24) may help explain the difference. The interaction of male sex with residence in Bei Duan village, although not statistically significant, suggests an uncontrolled risk factor, such as tobacco smoking

---

[4] M. Gail, personal communication.

(25), which is disproportionately more common among men in Bei Duan.

References

1. Li, J. Y., Liu, B. Q., Chen, Z. J., Sun, X. D., and Rong, S. D. Atlas of cancer mortality in the People's Republic of China. Int. J. Epidemiol., *10:* 127–133, 1981.

2. You, W-c., Zhang, L., Gail, M. H., Ma, J. L., Chang, Y. S., Blot, W. J., Li, J. Y., Zhao, C. L., Liu, W. D., Li, H. Q., Hu, Y. R., Bravo, J. C., Correa, P., Xu, G. W., and Fraumeni, J. F., Jr. *Helicobacter pylori* infection, garlic intake, and precancerous lesions in a Chinese population at low risk of gastric cancer. Int. J. Epidemiol., *27:* 941–944, 1998.

3. Forman, D., Sitas, F., Newell, D. G., Stacey, A. R., Boreham, J., Peto, R, Campbell, T. C., and Chen, J. Geographic association of *Helicobacter pylori* antibody prevalence and gastric cancer mortality in rural China. Int. J. Cancer, *46:* 608–611, 1990.

4. Zhang, L., Blot, W. J., You, W-c., Chang, Y. S., Kneller, R. W., Jin, M. L., Li, J. Y., Zhao, L., Liu, W. D., Zhang, J. S., Ma, J. L., Samloff, M., Correa, P., Blaser, M. J., Xu, G. W., and Fraumeni, J. F., Jr. *Helicobacter pylori* antibodies in relation to precancerous gastric lesions in a high-risk Chinese population. Cancer Epidemiol. Biomark. Prev., *5:* 627–630, 1996.

5. Go, M. F., Kapur, V., Graham, D. Y., and Musser, J. M. Population genetic analysis of *Helicobacter pylori* by multilocus enzyme electrophoresis: extensive allelic diversity and recombinational population structure. J. Bacteriol., *178:* 3934–3938, 1996.

6. Yang, H., Wu, S. V., Pichuantes, S., Song, M., Wang, J., Zhou, D., Xu, Z., Quan, S., Polito, A., and Walsh, J. H. High prevalence of *cagA*-positive strains in *Helicobacter pylori*-infected, healthy, young Chinese adults. J. Gastroenterol. Hepatol., *14:* 476–480, 1999.

7. Ito, Y., Azuma, T., Ito, S., Miyaji, H., Hirai, M., Yamazaki, Y., Sato, F., Kato, T., Kohli, Y., and Kuriyama, M. Analysis and typing of the *vacA* gene from *cagA*-positive strains of *Helicobacter pylori* isolated in Japan. J. Clin. Microbiol., *35:* 1710–1714, 1997.

8. Shimoyama, T., Fukuda, S., Tanaka, M., Mikami, T., Saito, Y., and Munakata, A. High prevalence of the *cagA*-positive *Helicobacter pylori* strains in Japanese asymptomatic patients and gastric cancer patients. Scand. J. Gastroenterol., *32:* 465–468, 1997.

9. Tummuru, M. K., Cover, T. L., and Blaser, M. J. Cloning and expression of a high-molecular-mass major antigen of *Helicobacter pylori*: evidence of linkage to cytotoxin production. Infect. Immun., *61:* 1799–1809, 1993.

10. Covacci, A., Censini, S., Bugnoli, M., Petracca, R., Burroni, D., Macchia, G., Massone, A., Papini, E., Xiang, Z., Figura, N., *et al*. Molecular characterization of the 128-kDa immunodominant antigen of *Helicobacter pylori* associated with cytotoxicity and duodenal ulcer. Proc. Natl. Acad. Sci. USA, *90:* 5791–5795, 1993.

11. Kuipers, E. J., Perez-Perez, G. I., Meuwissen, S. G. M., and Blaser, M. J. *Helicobacter pylori* and atrophic gastritis: importance of the CagA status. J. Natl. Cancer Inst., *87:* 1777–1780, 1995.

12. Blaser, M. J., Perez-Perez, G. I., Kleanthous, H., Cover, T. L., Peek, R. M., Chyou, P. H., Stemmermann, G. N., and Nomura, A. Infection with *Helicobacter pylori* strains possessing *cagA* is associated with an increased risk of developing adenocarcinoma of the stomach. Cancer Res., *55:* 2111–2115, 1995.

13. Parsonnet, J., Friedman, G. D., Orentreich, N., and Vogelman, H. Risk for gastric cancer in people with *cagA* positive or *cagA* negative *Helicobacter pylori* infection. Gut, *40:* 297–301, 1997.

14. You, W-c., Zhang, L., Gail, M. H., Li, J. Y., Chang, Y. S., Blot, W. J., Zhao, C. L., Liu, W. D., Li, H. Q., Ma, J. L., Hu, Y. R., Bravo, J. C., Correa, P., Xu, G. W., and Fraumeni, J. F., Jr. Precancerous lesions in two counties of China with contrasting gastric cancer risk. Int. J. Epidemiol., *27:* 945–948, 1998.

15. Chinese Association of Gastric Cancer. Classification and Diagnostic Criteria for the Histologic Gastric and Duodenal Biopsy Specimens, pp. 3–5. Liaoning, China: Liaoning Publishing House, 1981.

16. You, W-c., Blot, W. J., Li, J. Y., Chang, Y. S., Jin, M. L., Kneller, R., Zhang, L., Han, Z. X., Zung, X. R., Liu, W. D., Zhao, L., Correa, P., Fraumeni, J. F., Jr., and Xu, G. W. Precancerous gastric lesions in a population at high risk of stomach cancer. Cancer Res., *53:* 1317–1321, 1993.

17. You, W-c., Li, J. Y., Blot, W. J., Chang, Y. S., Jin, M. L., Gail, M. H., Zhang, L., Liu, W. D., Ma, J. L., Hu, Y. R., Mark, S. D., Correa, P., Fraumeni, J. F. Jr., and Xu, G. W. Evolution of precancerous gastric lesions in a rural Chinese population at high risk of gastric cancer. Int. J. Cancer, *83:* 615–619, 1999.

18. Perez-Perez, G. I., Dworkin, B. M., Chodos, J. E., and Blaser, M. J. *Campylobacter pylori* antibodies in humans. Ann. Intern. Med., *109:* 11–17, 1988.

19. Groves, F. D., Zhang, L., Li, J. Y., You, W-c., Chang, Y. S., Zhao, L., Liu, W. D., Rabkin, C. S., Perez-Perez, G. I., Blaser, M. J., and Gail, M. H. Comparison of two enzyme-linked immunosorbent assay tests for diagnosis of *Helicobacter pylori* infection in China. Cancer Epidemiol. Biomarkers. Prev., *6:* 551–552, 1997.

20. Hook-Nikanne, J., Perez-Perez, G. I., and Blaser, M. J. Antigenic characterization of *Helicobacter pylori* strains from different parts of the world. Clin. Diagn. Lab. Immunol., *4:* 592–597, 1997.

21. Odenbreit, S., Puls, J., Sedlmaier, B., Gerland, E., Fischer, W., and Haas, R. Translocation of *Helicobacter pylori* CagA into gastric epithelial cells by type IV secretion. Science (Wash. DC), *287:* 1497–1500, 2000.

22. Fleiss, J. L. Statistical Methods for Rates and Proportions, p. 15. New York: John Wiley and Sons, 1973.

23. Kleinbaum, D. G. Logistic Regression: A Self-Learning Text, pp. 1–226. New York: Springer-Verlag, 1994.

24. You, W-c., Zhang, L., Pan, K. F., Jiang, J., Chang, Y. S., Perez-Perez, G. I., Liu, W. D., Ma, J. L., Gail, M. H., Blaser, M. J., Fraumeni, J. F., Jr., and Xu, G. W. *Helicobacter pylori* prevalence and CagA status among children in two counties of China with high and low risks of gastric cancer. Ann. Epidemiol., *11:* 543–546, 2001.

25. Kneller, R. W., You, W-c., Chang, Y. S., Liu, W. D., Zhang, L., Zhao, L., Xu, G. W., Fraumeni, J. F., Jr., and Blot, W. J. Cigarette smoking and other risk factors for progression of precancerous stomach lesions. J. Natl. Cancer Inst., *84:* 1261–1266, 1992.